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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,457	12/06/2000	Ian Popoff	RTS-0182	1220

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 05/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,457	POPOFF ET AL	
	Examiner	Art Unit	
	James D. Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of damage-specific DNA binding protein expression *in vitro*, does not reasonably provide enablement for antisense mediated inhibition of damage-specific DNA binding protein expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to compositions that inhibit the expression of Damage-specific DNA binding protein 1 and chemical modifications thereof, said language encompassing both *in vivo* and *in vitro* activity. The invention of the above claims is also drawn to methods of inhibiting the expression of or treating cells, tissues or animals having a condition associated with Damage-specific DNA binding protein 1 comprising contacting said cells or tissues or administering to animals the compound of claim 1 so that expression of damage-specific DNA binding protein 1 is inhibited.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of oligo and gene therapy is highly unpredictable.

Such unpredictability is due to obstacles that still face oligo therapy, as summarized here by Agrawas, who states the following: "(t)here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (Page 376); "[o]ligonucleotides must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. [c]ellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. [i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). Crooke also

points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (Pages 34-36).

Branch further elucidates the unpredictability of oligo therapy by stating that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column) and, "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns). Gewirtz et al. observes that the "antisense approach has generated controversy with regard to mechanisms of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased... to learn how they may be used successfully in the clinic (Page 3162, middle column, last paragraph). Branch concludes that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50). The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges in the oligo therapy art that are exemplified in the references above.

Further, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of Damage-specific DNA binding protein 1 expression *in vitro* as being correlative or representative of the successful *in vivo* use of antisense compounds or

treatment of any and/or all conditions or diseases suspected of being associated with Damage-specific DNA binding protein 1 expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the method claims is broad. Said claims are drawn to methods of treating or preventing any condition or disease, or cancers or hepatitis suspected of being associated with the expression of Damage-specific DNA binding protein 1 in an organism, comprising the administration of antisense oligonucleotides which specifically target and inhibit the expression of Damage-specific DNA binding protein 1. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of accessible target sites, modes of delivery, and most importantly, formulations to target appropriate cells and /or tissues harboring the target mRNA such that all Damage-specific DNA binding protein 1 expression is inhibited appropriately *in vivo*, and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with Damage-specific DNA binding protein 1 in an organism. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with Damage-specific DNA binding protein 1 in an organism, and since determination of these factors for a particular target gene in an organism is highly

unpredictable, one of ordinary skill in the art would be unable to practice the invention as presented in the specification over the scope claimed.

Furthermore, the instant specification fails to provide one of skill in the art guidance for the selection of pharmaceutical oligo compounds without undue trial and error experimentation since it is clear from the references above that in vitro and cellular screening do not correlate with pharmaceutical oligo compounds that function in an *in vivo* environment. The specification in general fails to provide adequate guidance to overcome the obstacles and unpredictability of oligo therapy that are exemplified in the references above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dualan et al., in view of Taylor et al., Baracchini et al., Milner et al., and Hayes et al.

Dualan et al. teach the nucleotide sequence encoding Damage-specific DNA binding protein 1 (abstract and GenBank accession number U18299). Dualan et al. do not teach antisense oligonucleotides that comprise internucleoside, sugar or nucleobase modifications, or chimeric antisense molecules, nor methods of inhibition using antisense oligos.

Taylor et al. teach the use of antisense oligos to inhibit any gene of known sequence, for therapeutic use or as a research tools for the elucidation of gene function.

Milner et al teach the screening of antisense oligonucleotides for their ability to inhibit a target gene of known sequence in vitro (See entire document).

Baracchini et al teach chimeric antisense as well as internucleoside, sugar or nucleobase modifications (column 6, line 18-column 8, line 56).

It would have been obvious to one of ordinary skill to design and use antisense molecules for the specific inhibition of Damage-specific DNA binding protein 1 expression, since the sequence for Damage-specific DNA binding protein 1 was taught previously by Dualan et al., and since Taylor et al. teaches that antisense oligonucleotides can be designed to inhibit any gene of known sequence. One of ordinary skill in the art would have been motivated to inhibit Damage-specific DNA binding protein 1 because Taylor et al. teach that such antisense inhibition is valuable as a research tool to elucidate gene function, and because Damage-specific DNA binding protein 1 has been implicated by Hayes et al. (applicant's IDS) in the repair of damaged DNA (page 248, para. 2, lines 13-17). One of ordinary skill in the art would have had a reasonable expectation of success of finding antisense sequences that inhibit Damage-specific

DNA binding protein 1 expression, because the methods for screening such antisense molecules had been taught previously by Milner et al. Furthermore, one of ordinary skill in the art would have been motivated to incorporate internucleotide, sugar and nucleobase modifications into such antisense molecules because it had been taught previously by Baracchini et al that such modifications enhance antisense stability and cellular uptake. One of ordinary skill in the art would have expected that the incorporation of such modifications into antisense molecules would render them less susceptible to nuclease degradation, as taught by Baracchini et al.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

J. Douglas Schultz, Ph.D.
May 2, 2002

ANDREW WANG
PRIMARY EXAMINER